



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/658,971 | 09/09/2003 | David Jonathan Madge | 2451.0090008 | 3998 |
| 26111 | 7590 | 07/25/2006 | EXAMINER | |
| STERNE, KESSLER, GOLDSTEIN & FOX PLLC 1100 NEW YORK AVENUE, N.W. WASHINGTON, DC 20005 | | | KWON, BRIAN YONG S | |
| | | | ART UNIT | PAPER NUMBER |

1614

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/658,971

Applicant(s)

MADGE ET AL.

Examiner

Brian S. Kwon

Art Unit

1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-116 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-116 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 1405, 09/19/05, 10/30/04, 09/17/04, 08/29/04, 03/18/04, 12/24/04
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election with the Group I Invention along with the sodium salt of cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)₂ as the elected species is acknowledged. Claims 27, 66, 71, 79-80, 96-97, 104, 106-107 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims. Claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-116 are currently pending for prosecution on the merits.

Claim Objections

2. Claim 24 is objected. Each claim should be ended by a period, not coma and period. "basic organic nitrogen containing compounds having a pK_b of about 7 or more,." should be corrected as "basic organic nitrogen containing compounds having a pK_b of about 7 or more."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 25-26, 47-57, 112-113 and 116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "reducing thrombin", "treating thrombosis" or treating deep vein thrombosis and/or pulmonary embolism, does not reasonably provide enablement for inhibiting thrombin in the treatment of prevention of diseases or preventing thrombosis, cardiovascular event, venous thromboembolic event, thromboembolic events or arterial diseases. The specification does not enable any person skilled in the art to which it

Art Unit: 1614

pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant claims are drawn to a parenteral pharmaceutical composition comprising a pharmaceutically acceptable base addition salt of a boronic acid derivatives and their use in inhibiting thrombin or treating or preventing thrombosis, cardiovascular event, thromboembolic events and arterial diseases. The American Heritage Dictionary (Second College Edition, 1982) defines the term "inhibit" as "to restrain or hold back; prevent; to prohibit; forbid etc..." and "prevent" as "to keep from happening; to keep from doing something". The interpretation of the instant claims allows for the prevention, cure, eradication or total elimination of thrombosis or any diseases or conditions associated with thrombosis by the administration of said compounds.

There are no known compounds of similar structure which have been demonstrated to prevent thrombosis or treatment of any disease or condition related to thrombosis. Since this assertion is contrary to what is known in medicine, proof must be provided that this

Art Unit: 1614

revolutionary assertion has merits. The existence of such a “magic bullet” is contrary to our present understanding of pharmacology. For example, there is no known cure for a disease or condition related to or complicated by thrombosis such as myocardial infarction, coronary heart disease, stroke and end stage renal disease. The true fact of the state of the art is illustrated succinctly in the “NIH Heart Disease & Stroke Research: Fact Sheet” (American Heart Association, 2004); “Cardiovascular Disease: Treatment for Stroke”, Stanford Hospital & Clinics, 2003; “Heart Disease”, Charlotte E. Grayson, WebMD, 2004; “Acute Congestive Heart Failure”, Thomas N. Levin, Postgraduate Medicine, Vol. 101, No. 1, 1997; “Chronic Renal Failure”, University of Pennsylvania Health System, www.pennhealth.com, 2005). Thus, it is beyond the skill of pharmacologists today to get an agent to be cure or completely eliminate the condition encompassed by the claimed invention.

The relative skill of those in the pharmaceutical art is high. The unpredictability of the pharmaceutical art is very high. As stated above, applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, “the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved”. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The claims are very broad. The scope of the instant claims encompasses the prevention (complete thwarting or warding off illness or total elimination or eradication) and the treatment of multiple complex disorders that may have unrelated manifestations including deep vein thrombosis, pulmonary embolism, coronary artery disease, heart valve disease, arrhythmia,

Art Unit: 1614

heart failure, stroke, shock, endocarditis, diseases of the aorta and its braches, disorders of the peripheral vascular systems, congenital heart diseases, angina (particularly chronic, stable angina pectoris), cardiomyopathy, restenosis, ischemic disease, thrombosis, pulmonary thromboembolism, cerebral thromboembolism, arteriovenous fistula, atheroembolism and etc...

The instant specification provides assays to test TRI 50c or TRI 50b in vitro and discloses that said compounds exhibit the reduction of platelet procoagulant activity (Examples 35, 36 and 38 and Table 2). Furthermore, the specification discloses in vivo activity of said compounds in reducing thrombosis formation. However, there is no demonstrated correlation that the tests and results apply to treatment or prevention all of the diseases or disorders embraced by the instant claims.

Although it is true that thrombosis or platelet aggregation may be involved in pathophysiology of multitude of diseases, for example coronary artery disease, heart valve disease, arrhythmia, heart failure, stroke, shock, endocarditis, diseases of the aorta and its braches, disorders of the peripheral vascular systems, congenital heart diseases, angina (particularly chronic, stable angina pectoris), cardiomyopathy, restenosis, ischemic disease, pulmonary edema associated with acute myocardial infarction, thrombosis, platelet aggregation, platelet adhesion, pulmonary thromboembolism, cerebral thromboembolism, arteriovenous fistula, atheroembolism, it is not know yet that a single underlying mechanism ties together all of the seemingly unrelated manifestations. Therefore, the skilled artisan would turn to undue amount of trial and error to find out which disease or condition would be response to the administration of the claimed boronic acid compounds.

Art Unit: 1614

Since the efficacy of said composition in inhibiting or preventing thrombin, thrombosis or diseases associated with thrombosis mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 16 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 16, it is not clear what is meant by "wholly or partially hydrogenated analogues thereof" and the specification does not define the term. Thus, one of ordinary skill in the art would not reasonably understand the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Regarding claim 24, there is no upper limit of pKb recited in the claim. The term "a pKb of about 7 or more" refers to any value greater than about 7. Claim 24 is vague and unclear and leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Claim Rejections - 35 USC § 103

Art Unit: 1614

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459

(1966), that are applied for establishing a background for determining obviousness under 35

U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Claeson (Biochem J., 1993) in view of Skordalakes (J Am Chem Soc., 1997), and further in view of Ketner (WO 94/21668), Wienand (WO 97/05161) and/or Shoichet (WO 00/35904).

Art Unit: 1614

Claeson teaches an organoboronic acid pinanediol ester inhibitor of thrombin having a neutral thrombin S1-binding moiety linked to a hydrophobic thrombin S2/S3-binding moiety, for example TRI 50b: Cbz-(R)-Phe-(S)-Pro-(R)-boroMpg Pinacol (abstract; Scheme 1; Results and Discussion).

Skordalakes is being supplied as a reference to demonstrate that the removal of pinacol ester would not alter the analogous thrombin inhibiting activity of the organoboronic acid.

Ketner is being supplied as a reference to demonstrate the routine knowledge in removing pinacol ester protecting groups by transesterification process to make boronic acid compound.

Wienand is being supplied as a reference to demonstrate the routine knowledge in preparing boronic acid derivatives represented by the formula I having thrombin inhibiting activity (i.e., free boronic acid and boronic acid ester) into various pharmaceutical dosage forms (i.e., parenteral or intravenous, oral, solution) and salts forms (page 9, lines 19-27 and Examples). Wienand also teaches use of said boronic acid formulation alone or in combination with other known cardiovascular drug (i.e., aspirin, heparin, t-PA, streptokinase, etc...) in treating thrombosis, for example deep vein thrombosis, pulmonary embolism, arterial thrombosis, for the control of coagulation and fibrinolysis, etc...(page 8, line 27 thru page 9, line 8; page 10, lines 10-15).

Shoichet is being supplied as a reference to demonstrate the routine knowledge in preparing boronic acid derivatives in various salt forms including alkali or alkaline earth salts (i.e., sodium salt). See page 8, lines 5-20.

Art Unit: 1614

The teaching of Claeson differs from the claimed invention in the use of (i) Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)₂, (ii) parenteral dosage form, for example intravenous injection, (iii) salt form, particularly sodium salt.

With respect to the selection of the instantly claimed Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)₂,

However, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to select the claimed compound (i.e., TRI 50c) with expectation (as taught by the combination of Skordalakes and Ketner) that the claimed compound prepared by removing pinacol ester protecting groups by transesterification process would not analogous properties of TRI 50b due to close structural similarity of the compounds. One having ordinary skill in the art would have been motivated to make such modifications because there is an increased interest in developing new low molecular weight inhibitors of thrombin having fewer side effects than those available (Claeson et al., pp. 311, col. 2, para. 2 and pp. 312 and Skordalakes et al., pp. 9936, last paragraph).

With respect to the instantly claimed parenteral formulation, for example intravenous injection, and in combination other cardiovascular agent,

The modified teaching of Claeson includes all that is recited in above discussion except for the preparation of said composition in parenteral formulation or “in a sealed container in the form of a finely divided solid, ready for reconstitution to form a liquid parenteral formulation” and co-administration with other known cardiovascular agent.

Art Unit: 1614

However, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to make such modification since Wienand teaches that the preparation of boronic acid derivatives into parenteral dosage forms or the co-administration of known cardiovascular agent is well within the skill of the artisan. One having ordinary skill in the art would have been motivated to make such modification to extend the usage of said composition in parenteral forms (or in a sealed container in the form of a finely divided solid, ready for reconstitution to form a liquid parenteral formulation) and in combination with other known cardiovascular agent to accommodate patient's preference and needs where the compliance could be improved with effective drug.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the instantly claimed sodium salt form,

The modified teaching of Claeson includes all that is recited in above discussion except for the preparation of said composition in sodium salt.

However, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to make such modification since both Wienand and Stoichet teach that the preparation of boronic acid derivatives into various salt forms including acid addition salt or alkaline metal salt is well within the skill of the artisan. One having ordinary skill in the art

Art Unit: 1614

would have been motivated to make such modification to extend the usage of said composition in the preferred salt forms, especially sodium salt, to maximize the efficacy of the drug.

As discussed in preceding comments, these types of modifications are deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. Thus, applicant has presented no evidence to establish the unexpected or unobvious nature of the claimed invention, and as such, claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-116 are properly rejected under 35 U.S.C. 103.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the- unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-24, 28-29, 40-46, 58-65, 67-70, 72-78, 81-95, 98-103, 105, 110, 114 and 115 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 19-23 and 28-36 of copending Application No. 10/937181 or claims 1-24 and 55-58 of copending Application No. 10/937854. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the determination of the claimed dosage forms (e.g., parenteral or intravenous) is considered within the skilled of the artisan especially in light of reading the referenced specification (particularly page 46, line 13 thru page 54, line 26 of 10/937181 and page 63, line 10 thru page 71, line 14 of 10/937854).

double patenting rejection since the conflicting claims have not yet been patented.

8. Claims 1-26, 28-65, 67-70, 72-78, 81-95, 98-103, 105 and 110-116 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-38 of copending Application No. 10/659179 or of copending Application No. 10/659178 which has been allowed. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claimed invention overlaps with the copending application. The determination of the specific dosage forms (e.g., parenteral or intravenous or oral) is considered within the skilled of the artisan especially in reading the referenced specification (particularly page 44, line 8 thru page 47, line 35 of 10/659179 or page 40, line 24 thru page 43, line 38 of 10/659178).

9. In looking in continuity data, it is noted that applicant has numerous pending applications encompassing the same or similar subject matter of the instant application. Applicant should review all subject matter considered the same or similar, and submit the appropriate Terminal Disclaimer(s). For example, Copending Application No. 11/077620 and Copending Application No. 11/078097 have same or similar subject matter(s).

Art Unit: 1614

Conclusion

10. No Claim is allowed.

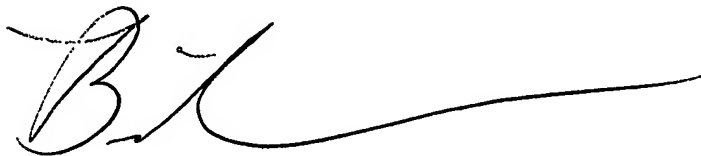
11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see <http://pair-direct.uspto.gov> Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
Patent Examiner
AU 1614

A handwritten signature in black ink, appearing to be 'BK' followed by a long horizontal flourish.